International Atomic Energy Agency

Production of Isotopes for Medical Applications: ^{99}Mo Status, Needs and Challenges

Workshop on 'Physics for Health in Europe'
Keynote Talk in Block 2: ^{99}Mo and alternatives

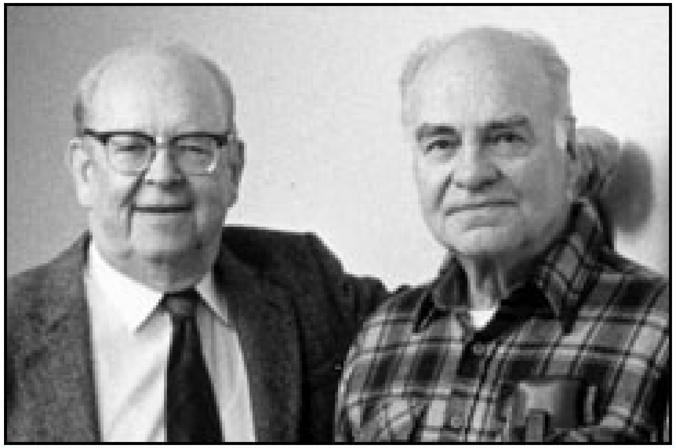
Natesan Ramamoorthy

CERN, Geneva, February 3, 2010

^{99}Mo (66 h) → ^{99m}Tc (6 h): Background

- ^{99m}Tc 6 h, decay by IT, Eγ 140.5 keV (89%); from ^{99}Mo-^{99m}Tc generator; ^{99m}Tc supplies from operations in house/central radiopharmacy
- >30 million studies/year; ~80% of diagnostic nuclear medicine (NM) imaging; **myocardial perfusion; bone mets** (renal, infection, others)
- Gold-standard generator uses fission-produced ^{99}Mo of high specific activity (~10^4 Ci/g) loaded on alumina column; elution of ^{99m}Tc in normal saline; 'kits' aid formulation of organ specific products.
- **^{99m}Tc reigning queen of radiopharmaceuticals for NM and hence ^{99}Mo is the queen mother!**

Discovery of ^{99m}Tc generator in 1957 in BNL



^{99m}Tc detected while refining ^{132}I from ^{132}Te → ^{99}Mo-^{99m}Tc generator → Stang, Tucker, Greene, Richards

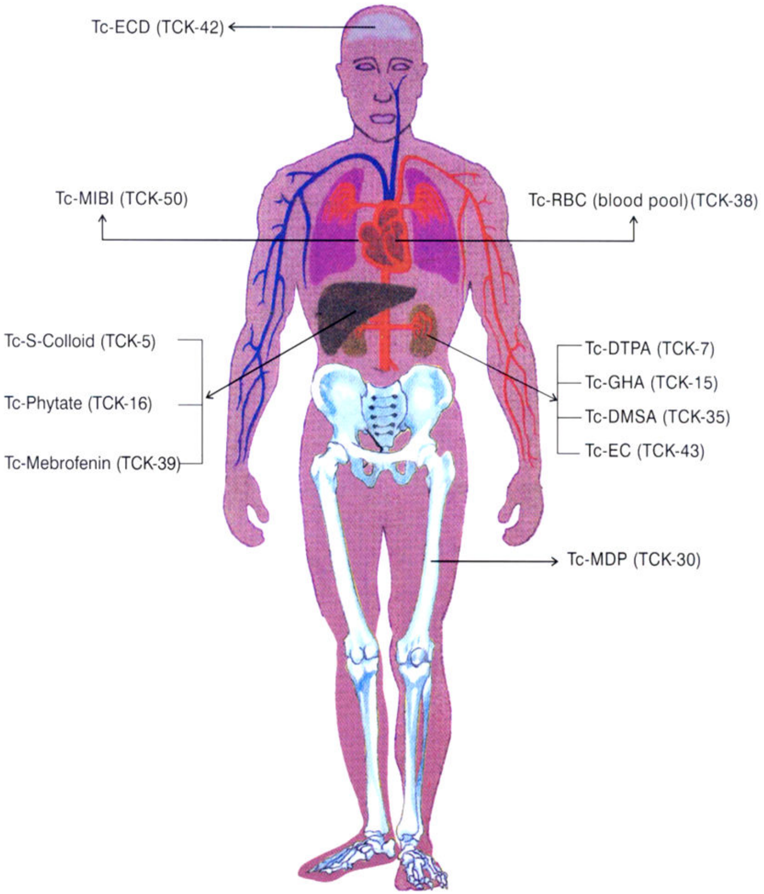
BNL declined to file a patent for this device - ^{99m}Tc generator!

- *<u>BNL memo in 1958</u>: "We are not aware of a potential market for technetium-99 great enough to encourage one to undertake the risk of patenting in hopes of successful and rewarding licensing."*

An Ode TO TECHNETIUM-99m *- by Rama 2007*

Time to sing of an isotope marvel
Over its saga of 50 year long travel;

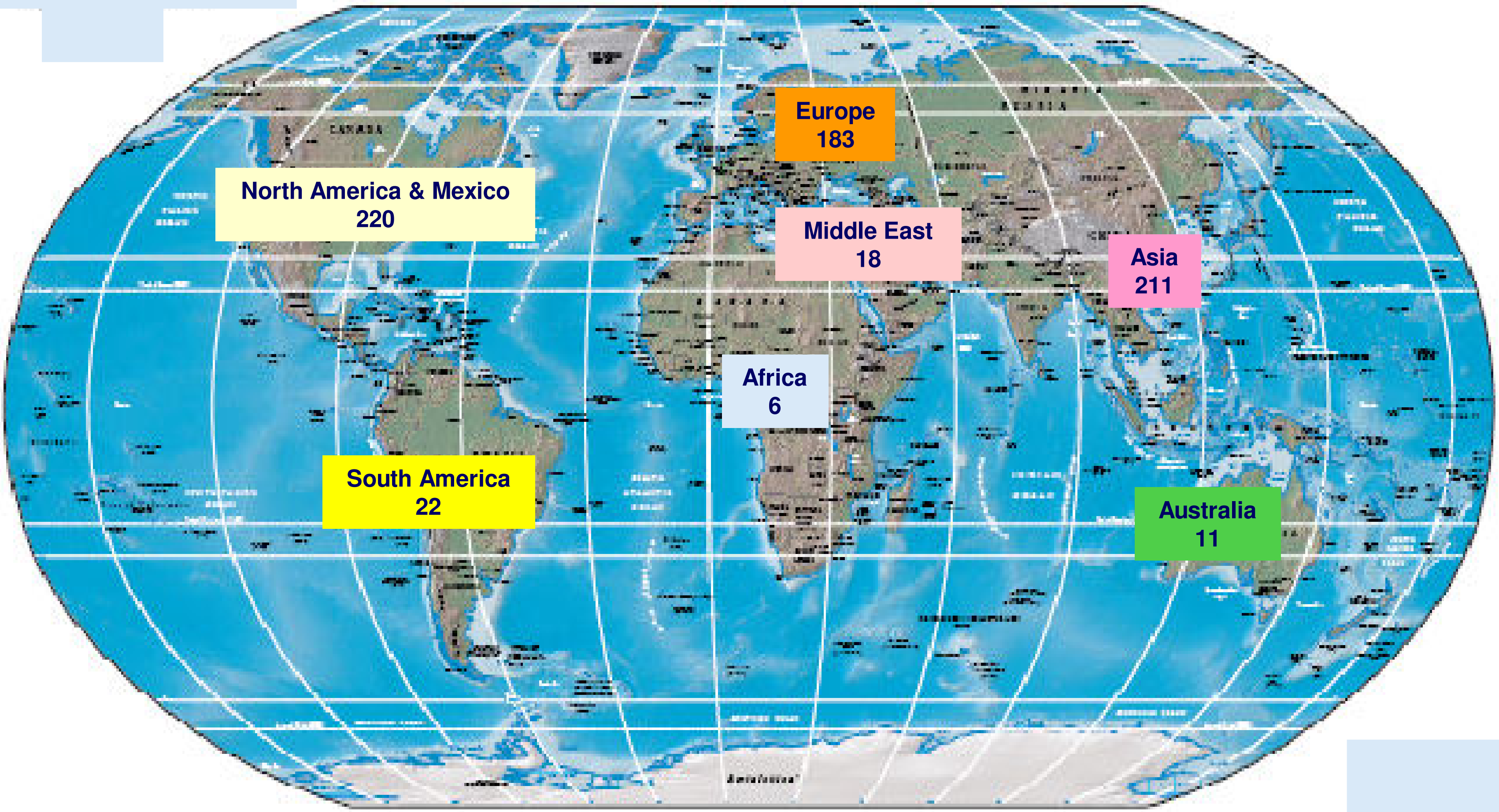
Technetium generator, kits like a rover
Endeavours galore, truly the world over;
Chemical, nuclear features the basics
Hefty synergy too of science classics
Nectarous growth then by any gauging
Enabling insights sans surgical ravaging
Tremendous impact on medical imaging;
IAEA successes, for sure in the cart *(in)*
Unravelling organ function of every part;
Medicinal gift from this artificial element,
99 metastable forever a Fine Ornament.



'Star' Radionuclides for SPECT and PET

- **^{99m}Tc** 6 h Eγ 140 keV
- from ^{99}Mo-^{99m}Tc generator; ^{99m}Tc supplies from operations in house/central radiopharmacy
- Ideal nuclear features for imaging (gamma camera, SPECT) and patient dose
- Versatile coordination chemistry of technetium
- Multi-disciplinary synergy → products for specific functional imaging
- Easy, abundant, economic availability ***(? since 2008***)

- **^{18}F** 110 min β^+ (0.635 MeV)
- ^{18}O(p,n) Ep 10-18MeV; 20-40uA
- Decentralised facilities for production and supplies
- Compatible to label organic and biological molecules or analogs
- Suitable for PET, PET-CT
- $T_{1/2}$ advantage over ^{11}C, ^{13}N, ^{15}O
- **Success of ^{18}FDG**
- several pharmaceuticals containing fluorine
- Relatively more expensive



Distribution of cyclotrons for production of PET tracers
(source: D. Schlyer, BNL/USA, based on inputs of 4 major manufacturers)

Access to ^{99m}Tc

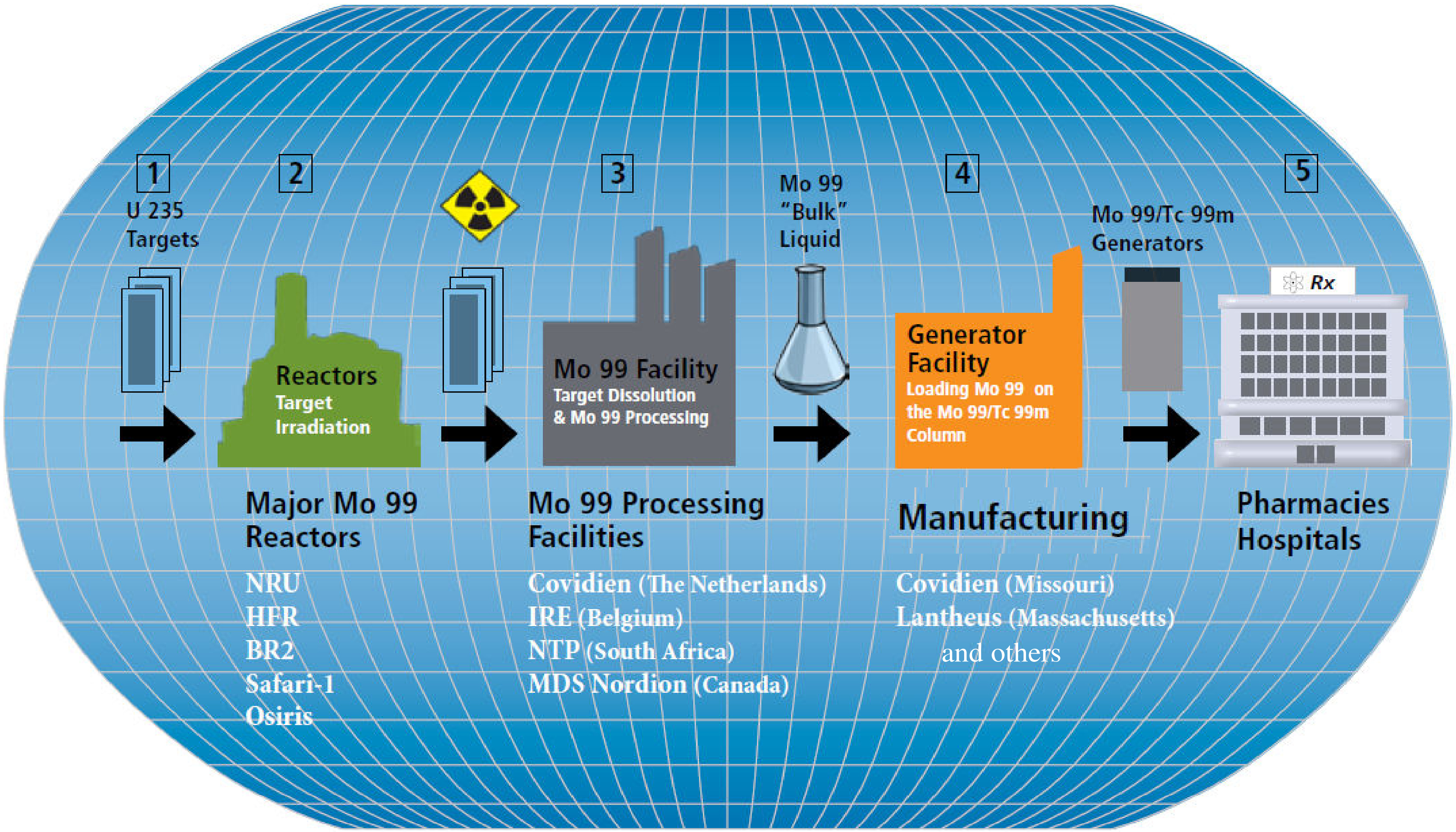
- ^{99m}Tc generators (0.2 to >10 Ci) produced by industry (100s - >1000 per week) & national labs (10 to 250+ per week); well-distributed production
- Supplies of 'bulk moly' easily available from the few main manufacturers (***? after Dec 2007***)
- IAEA support to MS in NM → ^{99}Mo-^{99m}Tc generators; import or domestic production
- Several MS availed IAEA support in establishing national production capacity for ^{99m}Tc generators; e.g. Bangladesh, Brazil, Iran, Philippines, Syria

^{99}Mo Production and Supplies

- Fission-based ^{99}Mo production: highly demanding technology; irradiation, processing, quality, safety, waste management, facilities → capital intensive – volumes
- **Fission ^{99}Mo**: **4** industrial producers using **5** aged reactors meeting over 95% ^{99}Mo world demands
- ^{99}Mo worldwide requirement: 450-500 TBq (>12000Ci, '6-day curies'); >95% ^{99}Mo produced with HEU targets; others: small-scale; ^{99}Mo to be shipped around the world every week, all through the year. *5th producer entry using LEU target and new reactor (OPAL-ANSTO)*
- Security concerns in HEU use → US initiatives of RERTR, GTRI → support to LEU technologies → Fission-based ^{99}Mo production: for long-term sustainability, efforts to shift to using LEU targets

Complex Supply-Utilisation Chain of ^{99}Mo

(source: from Covidien web site; modified to show generator producers)



^{99}Mo Production and Reactors in use

Country/Reactor	Producer	Operation p.a.	typical share
Canada/NRU	MDSN	315 d	40%
NL/HFR	IRE	290 d	10%
NL/HFR	Covidien	290 d	20%
Belgium/BR2	IRE	115 d	~5%
Belgium/BR2	Covidien	115 d	~5%
France/Osiris	IRE	220 d	~3%
SA/Safari1	NTP	315 d	10%
Argentina, Australia,	Russia, Indonesia,	others	<5%

Serious disruptions in ^{99}Mo supplies and follow-up events and actions

- ^{99}Mo production affected/shortages since end of 2007; NRU, HFR problems in 2008; NRU down since May 2009; HFR repairs from Mar 2010 → affects ^{99m}Tc gen availability
- Many international initiatives launched; in Europe, stakeholders seeking EC involvement
- Canadian Govt request to NEA-OECD in fall of 2008 to address issues → IAEA cooperation to all related activities
- OECD-NEA: Workshop in Paris, Jan 2009; Policy debate session, April 29, 2009 → HLG-MR formed – IAEA is Observer in HLG-MR; IAEA contributions to NEA events and HLG-MR; (i) Toronto June 2009; (ii) Paris Dec 2009
- 4-Member Panel of Canadian Govt → Report Dec 2009
- *(US-NAS report on feasibility of use of LEU Jan 2009)*

Points emerging from crisis in ^{99}Mo-^{99m}Tc supplies

- Scope and need for highly optimised use of all produced ^{99}Mo and capacity of ^{99m}Tc generators
- Mutual back-up plans among major producers for sustaining ^{99}Mo supplies cannot meet demands when more than one producer faces disruptions
- Complex supply chain with relatively low economic incentive for reactor services and ^{99}Mo production → unfavourable for fresh investments for long-term sustainability plans, new facilities etc
- ^{99}Mo cost is a small fraction in final cost of service to patient → additional cost of ^{99}Mo need not (should not) strongly impact final costs to patients

Findings from IAEA Consultancy Meeting, Warsaw:

Options for enhancing ^{99}Mo production/availability

Availing irradiation services in existing RR with suitable features and facilities → transport of irradiated HEU targets to the current processing facilities; 3 cases under consideration:

- Covidien, Petten-NL with MARIA reactor of IAE-POLATOM, Poland (target: Q1/Q2 2010)
- IRE, Fleurus-Belgium with FRM 2, Munich, Germany (target: by 2013; resources, approvals)
- IRE, Fleurus-Belgium with NRI, Rez, Czech Rep. (plans to be confirmed)

Findings from IAEA Consultancy Meeting, Warsaw: Plans for ^{99}Mo production in Europe

- **IAE-POLATOM, Poland**: plans to establish processing facility using locally irradiated LEU targets; meeting of advisory committees of Polish Nuclear Commission held on 1 Feb 2010; IAEA contributes relevant information
- **Romania/INR Pitesti**: scope for large capacity – seeking NNSA/US support – potential source for production using LEU targets by 2013
- EURASIA Isotopes Coalition (EIC): 3 reactors in Central Asia, 1 reactor in Czech + processing facility in Hungary + business advisory support

Scope and Opportunity for New Entrants

Possible Options

- Joint utilisation of an existing/new facility
- Partnership with a current major producer
- Engaging ^{99m}Tc generator manufacturers for a fixed share of purchasing ^{99}Mo from new source
- Stand-alone corporate venture

Challenges

- Competition and attitude of current players
- Bargaining power of generator producers
- Economic aspects

Alternate production routes for ^{99}Mo and ^{99m}Tc

^{99}Mo production

- **Fission route:** AHR (BWXT/US-Covidien); photo-fission of ^{238}U;
- **Reactor** route, non-fission: n,gamma with enriched ^{98}Mo - EIC; hot-atom chemistry using special target - Delft/NL; Mo metal target → gel - GE-Healthcare/US;
- **Accelerator/cyclotron** route: ^{100}Mo(γ,n); [*^{96}Zr(α,n)]* - with highly enriched targets; *nat abun 9.63%, 2.8%, respectively*

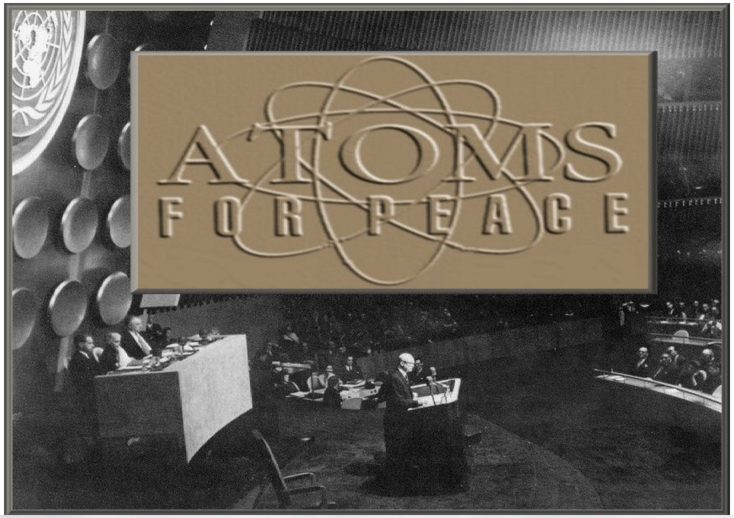
^{99m}Tc production

- ^{100}Mo(p,2n); very highly enriched targets; Ep 20-25MeV preferred (model: ^{18}F production-supplies)

^{99m}Tc separation from n,gamma ^{99}Mo

- Revisiting zirconium molybdate based gel generator technology
- High affinity adsorbents for Mo: PZC, PTC, nano-zirconia (cf. alumina); Japan, Australia, India
- Electrochemical separation of ^{99m}Tc - BARC/India (adopted from their ^{90}Sr-^{90}Y scheme)

International Atomic Energy Agency (IAEA)
‘Atoms for Peace’ Organization



- *The Agency shall seek **to accelerate and enlarge** the contribution of atomic energy to peace, **health** and prosperity **throughout the world**.*

Programme of Action for Cancer Treatment: The IAEA initiative to help combat cancer

- World Cancer Day on 4 February
- PACT - a new concept approach in the IAEA
- PACT partners in Geneva: WHO; UICC
- Nuclear Medicine (NM) utility was mainly for oncology for a long time (until myocardial perfusion imaging arrived).
- NM plays considerable role in managing cancer patients; Dx imaging for staging, monitoring efficacy, recurrence; Rx in certain cases; pain palliation of diffused bone mets.
- Bone scanning of cancer patients with ^{99m}Tc-medronate (MDP) is very widely performed all over the world.
- World Cancer Declaration (WCD): Please visit UICC web site to sign WCD at: www.uicc.org

IAEA Role and Support to ^{99}Mo Supplies

- Several plans of MS and industry, in different stages; at least some will progress to fruition in time. Different approaches and levels of support for short, medium and long term needed for sustainable reliability of ^{99}Mo supplies
- **IAEA role in addressing reliability and sustainability of ^{99}Mo supplies, including in developing countries**:
  - mobilising and fostering international cooperation in addressing all relevant issues
  - forum for engaging stakeholders, facilitating their meeting
  - help identify options, provide encouragement and foster partnerships and collaborations
  - creating awareness and collection - dissemination of information

Acknowledgements

- *All Colleagues and Collaborators - Past and Present*
- *CRP/TM Participants and their Management*
- Consultants and some industries for support in specific tasks/topics

Thank you all for attention

n.ramamoorthy@iaea.org

Need for a new facility in Europe – LEU-based production of ^{99}Mo

- HEU for civilian applications being phased out over the next several years (US bill cites 7-10 y)
- Conversion to using LEU targets for ^{99}Mo production needed (time, resources); plans for sustaining supplies during transition essential
- Need for augmenting current production capacity (moderately) to enhance back-up buffer availability
- Timely establishment of a new facility in Europe would help address all the above

Scope and Opportunity for IAE-Polatom

Strengths

- Already in radioisotope business – competencies and market knowledge
- Existing infrastructure including Maria reactor
- Producer and supplier of ^{99m}Tc generators

Challenges

- Competition with established players
- Economic aspects of supply chain
- Large commitment of resources; technologically demanding venture

IAEA support to addressing security of ^{99}Mo supplies for medical use

- MS seek support - information dissemination: status covered in IAEA Nuclear Technology Review (NTR 2009, 2010) and Annual Reports (2008, 2009); discussions in all IAEA Board Meetings in 2009, in other related events
- High interest in the ongoing IAEA CRP on LEU-based ^{99}Mo production (2005-2011) with 14 teams
- IAEA interactions with users in EANM-2008 (Munich) and through AIPES (since 2009); interactions continue with all stakeholders
- GC-2009 side event: *Reliability of supplies of medical isotopes produced in research reactors: Issues for regulators;* 76 participants from 34 MS attended
- Annex in NTR-2010 on ^{99}Mo to highlight all relevant issues, initiatives and challenges - draft under preparation

^{99}Mo Production – Established Methods

Fission Molybdenum

- ~6.1% fission yield
- enriched ^{235}U targets
- highly complex separation
- stringent purity needs
- waste handling
- elaborate infra-structure, and qualified personnel
- robust QA systems
- regulatory compliances
- capital intensive
- Corporate Activity

(n,γ) Molybdenum

- high purity MoO_3 targets
- high neutron flux (>5X10^{13} to 2X10^{14})
- large mass targets; RN impurities from trace contaminants
- suited for local and small-scale demands
- very limited use (~1%)
- mostly done in national centres

Findings from IAEA Consultancy Meeting, Warsaw:

n, gamma route of ^{99}Mo production

- Need to support $(n,\gamma)^{99}$Mo production, including gel and alternative generators – for meeting local/regional needs; useful addition to global supply by blending with fission-produced ^{99}Mo - for alumina column generators
- Japan, ROK interest in $(n,\gamma)^{99}$Mo cited in Paris; progress in plans reported to HLG-MR
- Russia: Dimitrovgrad reactor to utilise epithermal neutron flux for ^{98}Mo$(n,\gamma)^{99}$Mo (σ_{epi} 6.5 b) → higher sp. acty.
- Rosatom designated focal point in Russia for isotopes - delegation visit to IAEA on 30 June; further meeting likely in 2010 – more information on prospects in RF needed.